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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,568	05/15/2001	Samuel Bogoch	9425/46702	8438

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KENYON & KENYON
Suite 700
1500 K Street, N.W.
Washington, DC 20005

EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

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09/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/854,568	BOGOCH, SAMUEL	
	Examiner	Art Unit	
	David A. Saunders	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/4/07 & 6/23/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 7-13* is/are pending in the application.

4a) Of the above claim(s) *7-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

AMENDMENT ENTRY

Amendments of 4/4/07 and 6/26/07 have been entered. Claims 1-4 and 7-13 are pending. Claims 1-4 are under examination. The amendments have entered no new matter.

OBJECTION(S)/REJECTION(S) OF RECORD WITHDRAWN

The amendment has overcome previously stated issues as follows:

The objection to the specification.

The prior art rejection of claim(s) 5 based upon Bogoch (4,840,915), due to the cancellation of claim 5.

OBJECTION(S)/REJECTION(S) OF RECORD MAINTAINED

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Except for the issue pertaining to the crossing of the blood brain barrier by antibodies, the rejection of record is maintained in its essence. Even if the anti-malignin antibody that would be produced when the patient is actively immunized with administered malignin could cross the blood brain barrier, to some degree, it is considered that the following issues would remain.

Applicant has urged (amendment of 4/4/07 at page 6) that Example 8 of the specification teaches one how to stimulate production of anti-malignin antibody. The examiner does not concur, because Example 8 teaches one how to stimulate production of anti-recognin antibody, not of anti-malignin antibody. It is noted that

Example 8 teaches that Recognin is a 250,000 Dalton glycoprotein that is a precursor of malignin. One of skill would expect a macromolecule of such molecular weight to be immunogenic. The claims, however, call for administering malignin, not recognin, in order to stimulate production of anti-malignin antibody. It is noted that malignin is inherently a 16-mer peptide of a much lower molecular weight (examiner estimates this m.w. to be ~1,800, assuming that the amino acid residues have an average m.w. of 110). See para. [0003] and [0022] of US 2007/0160624 (cited on 892). One of skill would not expect a peptide of such lower molecular weight to be immunogenic. Rather, one would expect that such peptides would need to be chemically conjugated to a higher m.w. immunogenic carrier protein, or fused to a higher m.w. immunogenic carrier peptide/protein, or somehow complexed with/conjugated to a special adjuvant (e.g. an MHC construct, a HSP polypeptide, a dendrimeric construct). Example 8 is thus not considered to be enabling for showing one how to stimulate production of anti-malignin antibody by administering malignin.

The examiner also finds that the specification Examples (e.g. Example 5 showing in vitro cytotoxicity of the antibodies), as well the statements made by Dr. Bogoch in the 1.132 declaration filed on 4/4/07 (para. 18 at pages 5-6) regarding in vitro cytotoxicity , to be unconvincing. First of all, it is noted that specification Example 5 discloses results obtained with an anti-recognin antibody, not an anti-malignin antibody. As noted supra, Recognin is a 250,000 Dalton glycoprotein that is a precursor of malignin; Recognin thus would be expected to have epitopes that stimulate production of antibodies against the glycosyl moieties of this glycoprotein, in addition to or in lieu of antibodies directed

to the 16-mer peptide which constitutes malignin, per se. One thus has no idea whether the cytotoxicity demonstrated in Example 5 was due to the presence of anti-glycosyl antibodies or anti malignin peptide antibodies.

The examiner finds that numerous other statements made in the 1.132 declaration filed 4/4/07 concerning Example 5 are confusing and/or not relevant. For example, para. 11 (pages 3-4) refers to Example 5 of the application as showing that anti-malignin antibody was introduced intravenously in Wistar rats. The examiner finds that Example 5 only to cytotoxic effects measured in vitro.

The examiner notes that declarant has also referred to specification Example 1 as showing that anti-malignin antibody is cytotoxic to glioblastoma brain cancer cells (para. 18 at pages 5-6). The examiner, however, finds that specification Example 1 as showing that anti-malignin antibody is able to immunocytochemically stain, rather than kill, cancer cells. Again, Example 1 discloses results obtained with an anti-recognin antibody, not an anti-malignin antibody. Example 1 thus offers nothing to show that the instant invention was enabled.

The 1.132 declaration of Dr Bogoch has, likewise, urged (para. 19 at page 6) that Example 6 of the specification shows inhibition of the growth of cancer cells by anti-malignin antibody. Again the examiner finds that Example 6 discloses results obtained with an anti-recognin antibody, not an anti-malignin antibody. Further, the results in Example 6 show growth inhibition of small cell lung carcinoma cells, not of glioma cancer cells, as required by the claims. Additionally, the results in Example 6 show growth inhibition, not cytotoxicity against cancer cells, as required by the claims.

The 1.132 declaration of Dr Bogoch has urged (para. 21 at page 6) that numerous in vitro studies of glioma therapies have translated well for in vivo results. These urgings are unconvincing because they all involve other kinds of therapies (e.g. with chemotherapeutic agents, with passively administered antibody (not with antigen administered to actively induce antibody production) against antigens other than malignin. The Office thus considers such findings of no probative value with respect to immunization with malignin.

The 1.132 declaration of Dr Bogoch has urged (para. 21 at page 6) that declarant is unaware of "scientific literature available at the priority date of the application that teaches or suggests antibodies shown to have complement-dependent cytotoxicity in cancer cells in vitro are not also cytotoxic to the same type of cancer cells in vivo." The examiner finds such a mere negative statement to be unconvincing, in light of the overwhelming experience over the last century that, despite some promising in vitro results "cancer vaccines don't work." See Spitler, page 1, col. 1. Spitler teaches that "cancer vaccines don't work" because the tumor antigens have not been well characterized and because conventional adjuvants have been used (para. spanning cols. 1-2 of page 1). Spitler further teaches that cancer vaccines may be made to work, when the tumor antigens have chemically characterized and/or when improved adjuvants have been developed (page 2, col. 1). Applicant's disclosure is thus precisely at the point of development which Spitler has indicated that "cancer vaccines don't work" because the tumor antigens have not been well characterized and because conventional adjuvants have been used. Applicant's disclosure, for example, has not

Identified malignin as a 16-mer peptide. Applicant's disclosure has not taught how the 16-mer peptide that constitutes malignin might be better presented in the context of MHC molecules, how it might be better presented by dendritic cells, or how it might be combined with a better adjuvant.

Declarant has further urged (para. 23 at page 7) that dendritic cell based vaccines against glioma tumors have been developed since applicant's filing date. The Office considers such findings may be interesting; however, these dendritic cell based vaccines represent the further kind of work that Spliter suggested would be required, before there would be effective cancer vaccines. Such further development was not part of applicant's disclosure; the Office thus sees no reason to grant applicant the right to exclude others, based upon the paucity of information given in the disclosure that would have led one to develop an effective cancer vaccine, without further undue experimentation.

Applicant's urgings of 4/4/07 (page 4) and the 1.132 declaration (para. 15 and 16 at page 5) have made much of the fact that anti-malignin antibody can bind to human cancer tissues in vivo. Reference therein is made to Bogoch et al (Protides of the Biological Fluids, pp 337-362 1983, supplied as an exhibit). The Office position is that these studies show binding in vivo, but not killing of the cancer cells by the bound antibody, and that it is a leap of faith to conclude, from the in vitro cytotoxic studies, that there would be cytotoxicity in vivo. As far as the examiner can determine from Bogoch et al (Protides..), the anti-malignin antibody that binds in vivo was prepared by radiolabeling of anti-malignin antibody that had been produced by patients who naturally

had high levels of such antibody in their sera, not from patients who had been actively immunized with administered malignin, as in the claimed process. The Office does not consider that findings with an anti-malignin antibody, that had been produced naturally by patients, would necessarily correlate with those that would result when patients are actively immunized with administered malignin. This is because the anti-malignin antibody that had been produced naturally in the patients could have resulted from a different kind of presentation of the malignin antigen (e.g. it's naturally present on cell surfaces) to the patient's immune system, than would be the case when the patient is actively immunized with administered malignin. Note, for example, Ezzell (The Jour. of NIH Res., 7, 46-49, 1995, cited on from 892) teaches that potential tumor antigens may be identified by their association with heat shock proteins (HSPs). See page 46, col. 2. Presentation by HSPs has not been contemplated by applicant for the case in which the malignin antigen is administered as a vaccine. Since the anti-malignin antibody that had been produced naturally in the patients may be qualitatively different (e.g. recognize epitopes in a different way) from the anti-malignin antibody that would be produced when the patient is actively immunized with administered malignin, the Office does not consider that results showing the so called in vivo binding of administered anti-malignin antibody to be relevant. Further the Office does not consider that the anti-malignin antibody that had been produced naturally in the patients and which has been shown to correlate with a good prognosis (as in Bogoch et al (Protides..)) is necessarily qualitatively the same as the anti-malignin antibody that would be produced when the patient is actively immunized with administered malignin.

In summary, applicant has presented a three-pronged argument asserting that: (1) the present application teaches one of skill in the art how to subcutaneously administer malignin to produce antimalignin antibody *in vivo,* (2) the present application teaches that antimalignin antibody preferentially binds glioma cells in the brain *in vivo,* and (3) the present application teaches that antimalignin antibody kills glioma cells *in vitro* through at least complement-dependent cytotoxicity. As noted supra, Example 8 of the specification does not teach one how to stimulate production of anti-malignin antibody but, rather, of anti-recognin antibody. As noted supra, the anti-malignin antibody that had been produced naturally in the patients and which has been shown to localize in vivo to glioma cancer cells (Bogoch et al (Protides..)) is not necessarily qualitatively the same as the anti-malignin antibody that would be produced when the patient is actively immunized with administered malignin. As noted supra, the in vitro cytotoxicity data was obtained with an anti-recognin antibody and not with an anti-malignin antibody; further, one has no assurance that in vitro cytotoxicity correlates with in vivo cytotoxicity.

Applicant's arguments filed 4/4/07 have been fully considered but they are not persuasive for the above reasons.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

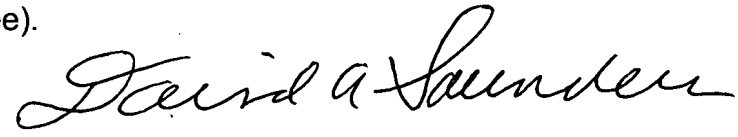
TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CONTACTS

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, whose telephone number is 571-272-0849. The examiner can normally be reached on Mon.-Thu. from 8:00 am to 5:30 pm and on alternate Fridays. The examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Typed 9/17/07 DAS



DAVID A. SAUNDERS
PRIMARY EXAMINER